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Gingival recession after scaling and root planing with or without systemic metronidazole and amoxicillin: a re-review

Kaufmann, Manuela E ; Wiedemeier, Daniel B ; Zellweger, Urs ; Solderer, Alex ; Attin, Thomas ; Schmidlin, Patrick R

Abstract: BACKGROUND Gingival recessions inevitably occur during healing after scaling and root planing, but synoptic data on this topic is still lacking. This review compared the recession formation with and without the administration of systemic antibiotics. OBJECTIVES To evaluate the formation of recession with and without the administration of antibiotics during the healing after scaling and root planing. MATERIALS AND METHODS This study re-analyzed publications that reported clinical attachment levels (CAL) and probing pocket depths (PD) up to January 2019, including the pivotal review by Zandbergen and co-workers (2013). Whereas these studies traditionally focused on PD and CAL, the present analysis compared recession formation (ΔREC) after adjunctive systemic administration of amoxicillin (amx) and metronidazole (met) during scaling and root planing (SRP) and SRP alone. The mean increase in ΔREC, if not reported, was calculated from CAL and PD values and statistically analyzed. Recession formation was compared after 3 and 6 months after therapy. Results were separately reported for chronic periodontitis (CP) as well as aggressive periodontitis (AP) cases. RESULTS Recessions increased consistently between baseline and follow-up. In the AP group, median ΔREC was 0.20 mm after 3 months, irrespective of whether antibiotics were administered or not. After 6 months, median ΔREC increased to 0.35 mm after AB and remained stable at 0.20 mm with SRP alone. In the CP group, after 3 months with and without antibiotics, median ΔREC accounted for 0.30 mm and 0.14 mm, respectively. After 6 months, median ΔREC accounted for 0.28 mm (with AB) and 0.20 mm (without AB). The quantitative assessment by meta-analyses also yielded small values (0.25 mm) for the estimated differences in recession formation between AB and noAB; however, none of them reached statistical significance. CONCLUSIONS Although a slight tendency towards higher recession formation after SRP in combination with AB could be observed in many studies, quantitative meta-analyses showed no clinically relevant difference in recession formation due to the administration of AB. In general, the description and discussion of recessions in the literature seems not to be a major focus so far. CLINICAL RELEVANCE Since the preservation of gingival tissues is important by preventive and therapeutic means, e.g., when avoiding postoperative root sensitivity or performing regenerative surgery, these aspects should not be neglected. We thus suggest to report REC measurements along with PD and CAL values for more direct recession formation (ΔREC) assessments in the future.

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Gingival recession after scaling and root planing with or without systemic metronidazole and amoxicillin: A re-review

Manuela E. Kaufmann[1*], Daniel B. Wiedemeier[3*], Urs Zellweger[2], Alex Solderer[1], Thomas Attin[1] and Patrick R. Schmidlin[1]

[1] Clinic of Conservative and Preventive Dentistry, Center of Dental Medicine, University of Zurich, Zurich, Switzerland

[2] Private practice, Praxis am Turm, Zug, CH-6300, Switzerland

[3] Statistical Services, Center of Dental Medicine, University of Zurich, Zurich, Switzerland

** Both authors contributed equally to this manuscript and share first authorship*

Address for correspondence:

Med. Dent. Manuela Kaufmann

University of Zurich

Clinic of Conservative and Preventive Dentistry

Center of Dental Medicine

Plattenstrasse 11 8032 Zurich

Phone: +41 44 634 34 17

E-mail: manuela.kaufmann@zzm.uzh.ch

Abstract

Background: Gingival recessions inevitably occur during healing after scaling and root planing, but synoptic data on this topic is still lacking. This review compared the recession formation with and without the administration of systemic antibiotics.

Objectives: To evaluate the formation of recession with and without the administration of antibiotics during the healing after scaling and root planing.

Materials and Methods: This study re-analyzed publications that reported clinical attachment levels (CAL) and probing pocket depths (PD) up to January 2019, including the pivotal review by Zandbergen and co-workers (2013). Whereas these studies traditionally focused on PD and CAL, the present analysis compared recession formation (∆REC) after adjunctive systemic administration of amoxicillin (amx) and metronidazole (met) during scaling and root planing (SRP) and SRP alone. The mean increase in ∆REC, if not reported, was calculated from CAL and PD values and statistically analyzed. Recession formation was compared after three and six months after therapy. Results were separately reported for chronic periodontitis (CP) as well as aggressive periodontitis (AP) cases.

Results: Recessions increased consistently between baseline and follow-up. In the AP group, median ∆REC was 0.20 mm after 3 months, irrespective of whether antibiotics were administered or not. After six months, median ∆REC increased to 0.35 mm after AB and remained stable at 0.20 mm with SRP alone. In the CP group, after three months with and without antibiotics, median ∆REC accounted for 0.30 mm and 0.14 mm, respectively. After six months, median ∆REC accounted for 0.28 mm (with AB) and 0.20 mm (without AB). The quantitative assessment by meta-analyses also yielded small values (≤ 0.25 mm) for the estimated differences in recession formation between AB and noAB, however, none of them reached statistical significance.

Conclusions: Although a slight tendency towards higher recession formation after SRP in combination with AB could be observed in many studies, quantitative meta-analyses showed no clinically relevant difference in recession formation due to the administration of AB. In general, the description and discussion of recessions in the literature seems not to be a major focus so far.

Clinical relevance: Since the preservation of gingival tissues is important by preventive and therapeutic means, e.g. when avoiding postoperative root sensitivity or performing regenerative surgery, these aspects should not be neglected. We thus suggest to report REC measurements along with PD and CAL values for more direct recession formation (ΔREC) assessments in the future.

Keywords: Scaling and root planing, debridement, clinical attachment level, periodontal healing, systemic antibiotics

Background

Recessions (REC) inevitably occur in the area of the inflamed gingival zone after thorough cleaning and in due course of successful healing, mainly due to the reduction of the swelling and shrinkage of the tissues [1]. Especially in severe cases with deep pockets, recession formation (∆REC) may be even accentuated. It has been shown that gingival REC increase from shallow pockets (≤ 3 mm) to moderately deep (4-6 mm) and deep sites (≥ 7 mm) from 1 mm over 1.2 to 1.9 mm, respectively [1], [2]. Studies have also shown that neither repeated instrumentation nor operator variability influence ∆REC [3], [4]. Flat surfaces on either single-rooted or flat molar teeth, however, show more REC than furcation-associated sites [5]. This illustrates the interplay between a lack of cleaning efficacy and cleaning accessibility and therefore decreased inflammation management and consequently less tissue shrinkage; vice versa, better cleaning (efficacy and accessibility) leads to more ∆REC. A plethora of strategies have been introduced including mechanical, physical and chemical adjuncts to improve the results after conventional SRP procedures. Among these suggested alternatives, no option has proven better efficacy or effectiveness so far than the adjunctive use of systemic antibiotics (AB) combination therapy like amoxicillin (amx) and metronidazole (met) for example [6]. Several systematic reviews and meta-analyses have impressively shown its superiority in this context so far; as well as for AP and CP [7]. However, most studies and reviews have mainly focused on PD and CAL and their respective losses, gains and the measurement of differences so far. These primary outcome parameters, however, still remain difficult to translate into clinically relevant treatment outcomes, especially if only means and standard deviations are depicted. Therefore, research has also focused on alternative measurements, such as the percentage of remaining pockets as such [8]. Unfortunately, the topic of ∆REC after non-surgical periodontal therapy has not yet gained much attention in this regard; especially not in the context of systemic AB usage. However, it might be of special clinical interest to oversee and estimate differences regarding ∆REC in the light of preventive and therapeutic considerations. For example in order to avoid postoperative root sensitivity and caries or when dealing with severe cases, which may still require surgical intervention after SRP including regenerative approaches. Particularly in the latter cases, any loss of marginal soft tissue should be considered as a shortcoming: The preservation of the marginal soft tissue height at facial and interproximal aspects remains of outmost clinical interest in order to achieve optimal clinical results, since any lost tissue is difficult to restore again and wound closure may be complicated.

Therefore, the aim of the present re-review was to investigate whether there are potential differences in ΔREC after administration of AB, i.e. amoxicillin (amx) and metronidazole (met) during SRP as compared to SRP alone. For this purpose, papers and data included in the meta-analysis by Zandbergen et al. [7] and other studies [9], [10], [11], [12], [13], [14], [15] were re-analyzed in order to calculate sensible estimates for REC values from PD and CAL measurements and quantitatively assess them by meta-analyses. The literature was updated and supplemented up to January 17th, 2019. Our working hypothesis was that the use of systemic AB would lead to increased ΔREC in both, CP and AP cases, 3 and 6 months after SRP.

Methods

The present re-review was based on the 28 studies, which were originally selected for inclusion in a systematic review by Zandbergen et al. [7]. This high-quality publication followed the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement) [16]. The original internet search included MEDLINE-PubMed, EMBASE and Cochrane-CENTRAL as databases. Language restrictions were set to English and Dutch. The focused question of the latter publication was adapted in the present study as follows:

„In patients with periodontitis what is the effect of adjunctive systemic administration of amx and met to SRP as compared to SRP alone with respect ΔREC?“

For details regarding quality assessment, data extraction and grading of the body of evidence, we also refer to the original article [7].

In addition to the existing review [7] an original internet search using identic search terms and databases was performed from April 1st, 2012 until January 17th, 2019. For specific search terms and search strategy, cf. Figure 1. The update of the systematic review was also conducted in accordance with the PRISMA guidelines [16]. Table 1 illustrates the characteristics of the included studies for meta-analysis (n = 16) and Table 2 shows summary statistics of the target variable ΔREC across the studies.

Data preparation

Data on original REC values were not available for most included studies. Therefore, mean recession REC at a given time was assessed as the difference between the reported mean clinical attachment level CAL and mean pocked depth PD, using the additive property of expectations $E(REC) = E(CAL - PD) = E(CAL) - E(PD)$. Hence, the mean recession

formation (ΔREC) between baseline (BL) and followup (FU) was calculated for each study for both groups (AB, noAB), again using the additivity property:

$$E(\Delta REC) = E(REC_{FU}) - E(REC_{BL}) \quad (1)$$

The variance for ΔREC for each study was assessed according to the equation of Bienaymé [17].

$$Var(\Delta REC) = Var(REC_{BL}) + Var(REC_{FU}) \quad (2)$$

Thus, our approach neglects potential covariance between CAL and PD, as well as between REC_{FU} and REC_{BL}, because these values were not reported and it would require patient-level information to estimate them correctly. However, the estimates for mean ΔREC are not affected, and merely the variances for ΔREC are potentially too large, i.e. potentially too conservative. We thus deemed these simple calculations appropriate for a first assessment of a potential antibiotic effect on REC, considering the current scarcity of data in the literature.

Meta-analyses

The calculated means and variances for ΔREC in combination with the respective sample sizes were then entered in a fixed and random effects meta-analysis model, using the metaphor package in R [18], [19].

Four separate meta-analyses for the mean difference in ΔREC ($\Delta REC_{noAB} - \Delta REC_{AB}$) between AB and noAB treatment were conducted: at 3 months and 6 months follow-up for the AP and the CP subset. In all cases, the heterogeneity parameter in the random effects model could not be satisfactorily assessed or was estimated to be zero, therefore the fixed effects model was chosen. Model assumptions were checked using residuals, funnel and radial plots.

Results

Considering the summary statistics (Table 2), REC increased consistently between baseline and follow-up. In the AP group, irrespective of whether AB were administered or not, median ΔREC was 0.20 mm. After six months, ΔREC increased to 0.35 mm with AB and remained stable at 0.20 mm with SRP alone. In the CP group after three months with AB and without AB, the median differences accounted for 0.30 mm and 0.14 mm, respectively. After six months, median ΔREC accounted for 0.28 mm (with AB) and 0.20 mm (without AB).

After 3 months, two out of five studies with AP showed slightly higher values for ΔREC without the use of AB, six out of seven considered studies dealing with CP showed more ΔREC when

using AB. After 6 months, five out of eight studies with AP and 2 out of five studies in the CP group showed larger ΔREC with AB.

None of the meta-analyses showed a significant effect with respect to the difference in ΔREC between AB and noAB treatment. In case of the AP group, the mean difference in ΔREC ($\Delta REC_{noAB} - \Delta REC_{AB}$) was estimated to be 0.17 mm (95% CI: -0.02, 0.35) after 3 months and -0.01 mm (95% CI: -0.19, 0.17) after 6 months, demonstrating a minimally larger REC increase for the noAB and AB group after the different follow-up times, respectively (Figure 3 [20], [21], [22], [23], [12] and 4 [20], [21], [22], [23], [14], [24], [25]). The differences between ΔREC for the CP group were estimated to be -0.25 mm (95% CI: -0.60, 0.09) after 3 months and -0.04 (95% CI: -0.43, 0.36) after 6 months, also not yielding any significant difference, but with a more accentuated pattern, which possibly suggests a slightly higher REC increase for the AB group (Figure 5 [26], [27], [15], [13], [11], [10], [9] and Figure 6 [15], [13], [11], [10], [9]). However, this pattern could also be due to a slight publication bias as the smallest studies show the largest effects (cf. Figure 5). Using the meta-analysis approach, the estimated differences in ΔREC between AB and noAB were thus always small, i.e. ≤ 0.25 mm.

Discussion

This re-review calculated the ΔREC from available PD and CAL values in the literature and compared non-surgical periodontal therapy with systemic AB (amoxicillin/metronidazole) to SRP alone after 3 and 6 months for CP and AP cases. Moreover, respective meta-analyses were conducted to quantitatively assess the potential differences in ΔREC.

The data set in this study comprised studies of a previously published meta-analysis [7], which served as the basis for our re-analysis. Notably, the underlying set of literature was identical but in the present study we focused on the REC outcome parameter, which was unfortunately not directly assessed so far, neither in the included individual studies nor – as a consequence – in other reviews. The data on REC first had to be calculated from the reported CAL and PD measurements, i.e. from the differences between these two parameters. Accepting relatively conservative standard errors, the statistical methodology to achieve the clinical parameter of ΔREC over time was straightforward.

As a general finding, a slight tendency towards higher ΔREC after SRP in combination with AB was found as compared to SRP alone in many studies. However, using the meta-analyses, estimated differences between the use of AB and noAB with regard to ΔREC yielded rather small

values for the estimated difference between the treatments, and none of them reached statistical significance. At first sight, the difference between the SRP treatment with and without AB would therefore not appear to be clinically relevant, since the largest estimated difference in ΔREC was only 0.25 mm (between AB and noAB in CP after 3 months). Nevertheless, the calculated differences should be related to the overall PD reduction and the additional CAL gain with observed mean values of -0.47 mm and +0.33 mm, respectively [28]. These values were also below 0.5 mm and one should acknowledge in this context the fact that the results are based on calculations related to multiple (also non-diseased) sites, which may dilute the actual effect.

In general, ΔREC after non-surgical therapy depends on the initial PD and may slightly increase during maintenance over time [29]. Long-term studies showed that REC decreased again over time, especially after surgical treatment [30]. The present study was limited to 3 and 6 months. However, from a clinical perspective, this time frame is relevant after non-surgical therapy, at least in terms of further decision making and most probably also in view of the initial tissue response and tissue shrinkage [2], [1]. The systemically determined difference between the AB and noAB treatment was shown to be rather small with absolute values around 0.00 - 0.25 mm, although in practice, the clinical outcome may strongly depend on the type of patient and diagnosis and thus show large inter-patient variability. Unfortunately, there is very little published data available from directly measurements and reporting REC after SRP. A study in CP patients reported ΔREC values after 3 and 6 months after non-surgical therapy with AB of 2.2 and 2.0 mm and 1.5 and 1.4 mm without AB [31].

Within the limitations of our re-review, the results should be interpreted with caution due to the presence of uncontrolled confounding factors in the included studies such as different dosage and time of the AB or unreported smoking status of the patients.

In summary, reporting REC values still seems to be of minor interest to researchers, except in studies where regenerative products are used and where REC appears more appropriate as a relevant surrogate parameter for shrinkage and tissue height. In our opinion, REC represents an important and valuable measure for judging the clinical outcome of any successful periodontal therapy. The unavoidable side-effect of the healing process, i.e. recession formation, may even lead to a reduction of patient's perception of oral health related quality of life (OHQoL) [32]. Patients only realize what the esthetic outcome of recession formation (papilla loss (aesthetics), dentin hypersensitivity or enhanced risk of root caries) means for them personally once

treatment is completed and additional therapy needs may emerge. Also, for clinicians, it is quite a daunting task to balance the therapy goals with acceptable endpoints for the individual patient regarding recession. Therefore, we recommend further investigations in this direction and adequate reporting on this relevant periodontal parameter as well. More original data and respective reviews are still warranted and further research on this topic may lead to new insights as well as optimized treatments in view of esthetic outcomes.

Conclusion

Although a slight tendency towards higher ΔREC after SRP in combination with AB could be observed as compared to SRP alone in many studies, quantitative meta-analyses showed no clinically relevant difference in ΔREC due to the administration of AB. Since the preservation of (healthy) gingival tissues is one of the major therapeutic goals in periodontology and is also important by preventive and therapeutic means, the aspect of ΔREC should not be neglected. We thus suggest to report REC measurements along with PD and CAL values in future studies as its indirect, mathematical assessment is cumbersome and less precise than when reported directly.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study, formal consent is not required.

Availability of data and materials

All relevant data supporting the conclusion of this article are within or mentioned in the manuscript.

Authors' contributions

PRS conceived the study and supervised the study. DW did the statistical evaluation of the papers and participated in its design. MK did the literature search. MK, AS and UZ drafted the manuscript. TA helped to supervise the methodological correctness of the performed study and the coordination. All authors carefully read and approved the final text.

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References

1. ADRIAENS, P. A., AND L. M. ADRIAENS. 2004. EFFECTS OF NONSURGICAL PERIODONTAL THERAPY ON HARD AND SOFT TISSUES. *PERIODONTOL 2000* 36: 121-145.
2. COBB, C. M. 1996. NON-SURGICAL POCKET THERAPY: MECHANICAL. *ANN PERIODONTOL* 1: 443-490.
3. BADERSTEN, A., R. NILVEUS, AND J. EGELBERG. 1984. EFFECT OF NONSURGICAL PERIODONTAL THERAPY. III. SINGLE VERSUS REPEATED INSTRUMENTATION. *J CLIN PERIODONTOL* 11: 114-124.
4. BADERSTEN, A., R. NILVÉUS, AND J. EGELBERG. 1985. EFFECT OF NON-SURGICAL PERIODONTAL THERAPY (IV). OPERATOR VARIABILITY. *J CLIN PERIODONTOL* 12: 190-200.
5. CLAFFEY, N., K. NYLUND, R. KIGER, S. GARRETT, AND J. EGELBERG. 1990. DIAGNOSTIC PREDICTABILITY OF SCORES OF PLAQUE, BLEEDING, SUPPURATION AND PROBING DEPTH FOR PROBING ATTACHMENT LOSS. 3 1/2 YEARS OF OBSERVATION FOLLOWING INITIAL PERIODONTAL THERAPY. *J CLIN PERIODONTOL* 17: 108-114.
6. MOMBELLI, A. 2018. MICROBIAL COLONIZATION OF THE PERIODONTAL POCKET AND ITS SIGNIFICANCE FOR PERIODONTAL THERAPY. *PERIODONTOL 2000* 76: 85-96.
7. ZANDBERGEN, D., D. E. SLOT, C. M. COBB, AND F. A. VAN DER WEIJDEN. 2013. THE CLINICAL EFFECT OF SCALING AND ROOT PLANING AND THE CONCOMITANT ADMINISTRATION OF SYSTEMIC AMOXICILLIN AND METRONIDAZOLE: A SYSTEMATIC REVIEW. *J PERIODONTOL* 84: 332-351.
8. KOLAKOVIC, M., U. HELD, P. R. SCHMIDLIN, AND P. SAHRMANN. 2014. AN ESTIMATE OF POCKET CLOSURE AND AVOIDED NEEDS OF SURGERY AFTER SCALING AND ROOT PLANING WITH SYSTEMIC ANTIBIOTICS: A SYSTEMATIC REVIEW. *BMC ORAL HEALTH* 14: 159.
9. THEODORO, L. H., N. Z. ASSEM, M. LONGO, M. L. F. ALVES, C. DUQUE, R. N. STIPP, N. L. VIZOTO, AND V. G. GARCIA. 2018. TREATMENT OF PERIODONTITIS IN SMOKERS WITH MULTIPLE SESSIONS OF ANTIMICROBIAL PHOTODYNAMIC THERAPY OR SYSTEMIC ANTIBIOTICS: A RANDOMIZED CLINICAL TRIAL. *PHOTODIAGNOSIS PHOTODYN THER* 22: 217-222.
10. BORGES, I., M. FAVERI, L. C. FIGUEIREDO, P. M. DUARTE, B. RETAMAL-VALDES, S. C. L. MONTENEGRO, AND M. FERES. 2017. DIFFERENT ANTIBIOTIC PROTOCOLS IN THE TREATMENT OF SEVERE CHRONIC PERIODONTITIS: A 1-YEAR RANDOMIZED TRIAL. *J CLIN PERIODONTOL* 44: 822-832.
11. COSGAREA, R., R. JUNCAR, C. HEUMANN, R. TRISTIU, L. LASCU, N. ARWEILER, A. STAVROPOULOS, AND A. SCULEAN. 2016. NON-SURGICAL PERIODONTAL TREATMENT IN CONJUNCTION WITH 3 OR 7 DAYS SYSTEMIC ADMINISTRATION OF AMOXICILLIN AND METRONIDAZOLE IN SEVERE CHRONIC PERIODONTITIS PATIENTS. A PLACEBO-CONTROLLED RANDOMIZED CLINICAL STUDY. *J CLIN PERIODONTOL* 43: 767-777.
12. TAIETE, T., M. Z. CASATI, É. P. RIBEIRO, E. A. SALLUM, F. H. NOCITI JÚNIOR, AND R. C. CASARIN. 2016. AMOXICILLIN/METRONIDAZOLE ASSOCIATED WITH NONSURGICAL THERAPY DID NOT PROMOTE ADDITIONAL BENEFITS IN IMMUNOLOGIC PARAMETERS IN GENERALIZED AGGRESSIVE PERIODONTITIS: A RANDOMIZED CONTROLLED CLINICAL TRIAL. *QUINTESSENCE INT* 47: 281-292.
13. MIRANDA, T. S., M. FERES, P. J. PEREZ-CHAPARRO, M. FAVERI, L. C. FIGUEIREDO, N. S. TAMASHIRO, M. F. BASTOS, AND P. M. DUARTE. 2014. METRONIDAZOLE AND AMOXICILLIN AS ADJUNCTS TO SCALING AND ROOT PLANING FOR THE TREATMENT OF TYPE 2 DIABETIC SUBJECTS WITH PERIODONTITIS: 1-YEAR OUTCOMES OF A RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL. *J CLIN PERIODONTOL* 41: 890-899.
14. LIRA, E. A., F. S. RAMIRO, F. M. CHIARELLI, R. R. DIAS, M. FERES, L. C. FIGUEIREDO, AND M. FAVERI. 2013. REDUCTION IN PREVALENCE OF ARCHAEA AFTER PERIODONTAL THERAPY IN SUBJECTS WITH GENERALIZED AGGRESSIVE PERIODONTITIS. *AUST DENT J* 58: 442-447.
15. FERES, M., G. M. SOARES, J. A. MENDES, M. P. SILVA, M. FAVERI, R. TELES, S. S. SOCRANSKY, AND L. C. FIGUEIREDO. 2012. METRONIDAZOLE ALONE OR WITH AMOXICILLIN AS ADJUNCTS TO NON-SURGICAL TREATMENT OF CHRONIC PERIODONTITIS: A 1-YEAR DOUBLE-BLINDED, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL. *J CLIN PERIODONTOL* 39: 1149-1158.
16. SHAMSEER, L., D. MOHER, M. CLARKE, D. GHERSI, A. LIBERATI, M. PETTICREW, P. SHEKELLE, L. A. STEWART, AND G. PRISMA-P. 2015. PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEW AND META-ANALYSIS PROTOCOLS (PRISMA-P) 2015: ELABORATION AND EXPLANATION. *BMJ* 350: G7647.
17. BIENAYMÉ, I.-J. 1853. *CONSIDÉRATIONS À L'APPUI DE LA DÉCOUVERTE DE LAPLACE SUR LA LOI DE PROBABILITÉ DANS LA MÉTHODE DES MOINDRES CARRÉS*. IMPRIMERIE DE MALLET-BACHELIER,
18. VIECHTBAUER, W. 2010. CONDUCTING META-ANALYSES IN R WITH THE METAFOR PACKAGE. *JOURNAL OF STATISTICAL SOFTWARE* 36:
19. TEAM, R. C. 2018. R: A LANGUAGE AND ENVIRONMENT FOR STATISTICAL COMPUTING. R FOUNDATION FOR STATISTICAL COMPUTING 2015, VIENNA, AUSTRIA.
20. AIMETTI, M., F. ROMANO, N. GUZZI, AND G. CARNEVALE. 2012. FULL-MOUTH DISINFECTION AND SYSTEMIC ANTIMICROBIAL THERAPY IN GENERALIZED AGGRESSIVE PERIODONTITIS: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL. *J CLIN PERIODONTOL* 39: 284-294.
21. VARELA, V. M., D. HELLER, M. X. SILVA-SENEM, M. C. TORRES, A. P. COLOMBO, AND E. J. FERES-FILHO. 2011. SYSTEMIC ANTIMICROBIALS ADJUNCTIVE TO A REPEATED MECHANICAL AND ANTISEPTIC THERAPY FOR AGGRESSIVE PERIODONTITIS: A 6-MONTH RANDOMIZED CONTROLLED TRIAL. *J PERIODONTOL* 82: 1121-1130.
22. HELLER, D., V. M. VARELA, M. X. SILVA-SENEM, M. C. TORRES, E. J. FERES-FILHO, AND A. P. COLOMBO. 2011. IMPACT OF SYSTEMIC ANTIMICROBIALS COMBINED WITH ANTI-INFECTIVE MECHANICAL DEBRIDEMENT ON THE MICROBIOTA OF GENERALIZED AGGRESSIVE PERIODONTITIS: A 6-MONTH RCT. *J CLIN PERIODONTOL* 38: 355-364.

23. MESTNIK, M. J., M. FERES, L. C. FIGUEIREDO, P. M. DUARTE, E. A. LIRA, AND M. FAVERI. 2010. SHORT-TERM BENEFITS OF THE ADJUNCTIVE USE OF METRONIDAZOLE PLUS AMOXICILLIN IN THE MICROBIAL PROFILE AND IN THE CLINICAL PARAMETERS OF SUBJECTS WITH GENERALIZED AGGRESSIVE PERIODONTITIS. *J CLIN PERIODONTOL* 37: 353-365.
24. DE LIMA OLIVEIRA, A. P., M. DE FAVERI, L. C. GURSKY, M. J. MESTNIK, M. FERES, A. D. HAFFAJEE, S. S. SOCRANSKY, AND R. P. TELES. 2012. EFFECTS OF PERIODONTAL THERAPY ON GCF CYTOKINES IN GENERALIZED AGGRESSIVE PERIODONTITIS SUBJECTS. *J CLIN PERIODONTOL* 39: 295-302.
25. XAJIGEORGIOU, C., D. SAKELLARI, T. SLINI, A. BAKA, AND A. KONSTANTINIDIS. 2006. CLINICAL AND MICROBIOLOGICAL EFFECTS OF DIFFERENT ANTIMICROBIALS ON GENERALIZED AGGRESSIVE PERIODONTITIS. *J CLIN PERIODONTOL* 33: 254-264.
26. MATARAZZO, F., L. C. FIGUEIREDO, S. E. CRUZ, M. FAVERI, AND M. FERES. 2008. CLINICAL AND MICROBIOLOGICAL BENEFITS OF SYSTEMIC METRONIDAZOLE AND AMOXICILLIN IN THE TREATMENT OF SMOKERS WITH CHRONIC PERIODONTITIS: A RANDOMIZED PLACEBO-CONTROLLED STUDY. *J CLIN PERIODONTOL* 35: 885-896.
27. SILVA, M. P., M. FERES, T. A. SIROTTO, G. M. SOARES, J. A. MENDES, M. FAVERI, AND L. C. FIGUEIREDO. 2011. CLINICAL AND MICROBIOLOGICAL BENEFITS OF METRONIDAZOLE ALONE OR WITH AMOXICILLIN AS ADJUNCTS IN THE TREATMENT OF CHRONIC PERIODONTITIS: A RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL. *J CLIN PERIODONTOL* 38: 828-837.
28. MDALA, I., I. OLSEN, A. D. HAFFAJEE, S. S. SOCRANSKY, M. THORESEN, AND B. F. DE BLASIO. 2014. COMPARING CLINICAL ATTACHMENT LEVEL AND POCKET DEPTH FOR PREDICTING PERIODONTAL DISEASE PROGRESSION IN HEALTHY SITES OF PATIENTS WITH CHRONIC PERIODONTITIS USING MULTI-STATE MARKOV MODELS. *J CLIN PERIODONTOL* 41: 837-845.
29. BADERSTEN, A., R. NILVEUS, AND J. EGELBERG. 1984. EFFECT OF NONSURGICAL PERIODONTAL THERAPY. II. SEVERELY ADVANCED PERIODONTITIS. *J CLIN PERIODONTOL* 11: 63-76.
30. KALDAHL, W. B., K. L. KALKWARF, K. D. PATIL, M. P. MOLVAR, AND J. K. DYER. 1996. LONG-TERM EVALUATION OF PERIODONTAL THERAPY: I. RESPONSE TO 4 THERAPEUTIC MODALITIES. *J PERIODONTOL* 67: 93-102.
31. MOMBELLI, A., P. BROCHUT, D. PLAGNAT, F. CASAGNI, AND C. GIANNOPOULOU. 2005. ENAMEL MATRIX PROTEINS AND SYSTEMIC ANTIBIOTICS AS ADJUNCTS TO NON-SURGICAL PERIODONTAL TREATMENT: CLINICAL EFFECTS. *J CLIN PERIODONTOL* 32: 225-230.
32. MENDEZ, M., P. D. MELCHIORS ANGST, A. F. STADLER, R. V. OPPERMANN, AND S. GOMES. 2017. IMPACTS OF SUPRAGINGIVAL AND SUBGINGIVAL PERIODONTAL TREATMENTS ON ORAL HEALTH-RELATED QUALITY OF LIFE. *INTERNATIONAL JOURNAL OF DENTAL HYGIENE* 15: 135-141.